third paragraph (planar), and p. 20, first paragraph (diverse polymers occupying different regions) and p. 18, paragraph (measuring a property of a population of polymers as a measure of efficiency of synthesis). Claim 1 has also been amended to remove the recital of a label. As the Examiner has noted, monomer components of probes can, in some circumstances, serve as an internal label. Thus, it is not always necessary to have an external label. Such a label is specified, however, in new dependent claim 39. Claim 10 has been amended in a similar manner to claim 1. Claim 10 is directed to methods for comparing two synthetic procedures for synthesizing an array of immobilized procedures. In such methods, two arrays of probe, each attached to a support via cleavable linkers, are synthesized by separate methods. Probes are cleaved from the two arrays to generate two separate mixtures of probes, and properties of these mixtures, such as an HPLC profile, are determined. Comparison of the properties indicates whether differences between the first and second synthesis procedures have any effect on efficiency. Unless otherwise indicated, claim amendments are for purposes of clarity. All claim amendments are made without prejudice, and are should not be construed as being an acquiescence in any remark in the office action.

Claims 1-15 stand rejected under 35 USC §103 as obvious over Pease in view of Reynolds for the same reasons as stated in the previous office action. The rejection is traversed as it applies to the pending claims.

Reynolds discusses a method of labelling an oligonucleotide with psoralalen that allows the oligonucleotide to become crosslinked to a complementary target, such as the bcr/abl mRNA associated with myelogenous leukemia. The goal of such methods is to inhibit translation of a given mRNA target. Oligonucleotides for use in such methods are synthesized in a conventional manner on an automated DNA synthesizer (p. 369, first column, fourth paragraph). In such synthesis, individual oligonucleotides are synthesized separately on particles. Such particle-bearing oligonucleotides are distinct from the array of

diverse polymers on a planar support, as now claimed. Individual oligonucleotides in Reynolds are separately cleaved from their supports, purified, labelled and used for their intended purpose (i.e., crosslinking to a target mRNA molecule).

Pease discusses synthesizing arrays of different oligonucleotides on a support using a photolithographic process. The arrays are used for analysis of a target nucleic acid. The pattern of hybridization of a labelled target nucleic acid to various probes within the array provides information as to the presence and nature of the target. Pease also discusses a quality control procedure for assessing the coupling efficiency of probes within the array. In this procedure, a labelled nucleoside is reacted with different regions of the array at different rounds of the oligonucleotide synthesis procedure. The substrate is scanned to determine the label attached at the different regions. The ratio of label between two regions at successive stages of the synthesis procedure is a measure of the coupling efficiency during a round of synthesis.

"Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." *In re Geiger,* 2 USPQ2d 1276 (Fed. Cir. 1987). The motivation must have sufficient "force" to "impel persons skilled in the art to do what applicant has done." *Ex parte Levengood,* 28 USPQ2d 1300, 1302 (BPAI 1993).

Here, neither of the cited references would have suggested combination with the other. In the Pease reference, the intended use of synthesized oligonucleotides in analyzing a target sequence requires that the oligonucleotides remain bound to the support during such use. Oligonucleotides lose spatial addressability and become useless for this task when they are cleaved from the array as a mixture. Further, the quality control method discussed by Pease involves attaching a labelling nucleoside to different regions of the array, and determining a ratio of fluorescence intensity between different regions of the

array. This type of assay would not be possible if the labelled nucleoside were cleaved from the array. Thus, neither Pease's intended use of oligonucleotides nor her quality control methods would have provided any motivation to synthesize probes on cleavable linkers or perform a quality control assay that involved cleavage of probes from such linkers.

In Reynolds, oligonucleotides are synthesized on cleavable linkers because the contemplated use of such oligonucleotides (i.e., inhibition of translation) requires that the oligonucleotides be available in solution. Reynolds' contemplated use is quite different from that of probe arrays, in which spatial addressability of probes on a support must be preserved to allow analysis of a target sequence. Accordingly, one seeking to synthesize an array of probes would have viewed Reynolds use of a cleavable linker as being mandated by Reynolds' intended use of his oligonucleotides, and would not have seen any relevance of such a linker to the quite different intended use of spatially addressable oligonucleotide arrays.

The office action seeks to compensate for the lack of motivation in the cited references by relying on certain knowledge asserted to be possessed by a person of ordinary skill in the art. Specifically, the office action states (at p. 5):

> One of ordinary skill would recognize that more than one linker could have been used such that release of only a portion of each member of the array for analytical purposes was done, thereby leaving the array still intact for other use. Alternatively, cleavage and analysis of the array complements following its use in detecting sequences may be done as the last portion of protocol for quality control purposes to ensure the array was appropriately synthesized; especially if negative results were reported. While the array would be destroyed in this alternative scenario, it would have already fulfilled the purpose applicant appears to believe it is limited to.

Taking the second statement first, applicants deny that cleaving probes from an array after using the array would have been viewed a desirable quality control measure that would have motivated one to synthesize probes on cleavable linkers, as

claimed. One problem of performing a quality control assay in this manner is that one would not discover potential synthesis problems until the array had already been used, perhaps hundreds of times. By this time, inaccurate results from the use of array, e.g., on clinical samples, might have had serious consequence. A second problem is that in performing a quality control after using a probe array, one could not distinguish between erosion of probes during use and incomplete synthesis. In view of these problems, one would not have been motivated to include cleavable linkers to determine the quality of a probe array after it had been used for its intended purpose

The Examiner's first statement of motivation attributed to one skilled in the art assumes that one would have realized that performing a measurement on a mixture of different cleaved probes would have been a useful measure of the efficiency of probes that remain on the surface. In fact, such was not obvious. Once probes have been cleaved to form a mixture of different probes, one can no longer assess properties of individual probes. Rather, one can only measure properties of a population, such as charge or molecular weight distribution throughout the population. It was not intuitively obvious that such properties for a population of probes could be interpreted as a useful measure of the efficiency of a synthesis procedure producing arrays of spatially addressable probes, and thereby of the quality of arrays resulting from such a process.

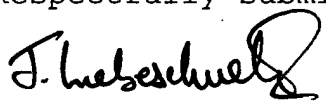
Moreover, the above statements of motivation are critical to the office action's case of obviousness, but are not present in the cited art. Thus, these statements appear to reflect the benefit of hindsight from reading applicants' disclosure. Applicants challenge the statements attributed by the Examiner to one of ordinary skill in the art, and respectfully request that the Examiner cite appropriate prior art for such statements in accordance with MPEP §2144.03, or withdraw the rejection. If the Examiner cites any references, applicants request that the final rejection be withdrawn to give applicants an opportunity to distinguish them.

In summary, no cognizable motivation has been provided for combining selected elements from Pease (arrays of polymers and quality control) with selected elements from Reynolds (cleavage) to achieve the claimed methods. As the Federal Circuit has cautioned, a "person of ordinary skill is the art is...*presumed to be one who thinks along the lines of conventional wisdom in the art...*," *Standard Oil Co. vs. American Cyanamid Co.*, 774 F.2d 448 (Fed. Cir. 1985), at p. 454 (emphasis supplied). The synthesis of elements from diverse sources in developing new advantageous methods is not the province of such an artisan, but rather indicates true invention.

The office action provides additional remarks concerning dependent claims 2, 4, 5, 10, and 12, 37 and 38. These claims are patentable for at least the same reasons as claim 1.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (650) 326-2400.

Respectfully submitted,



Joe Liebeschuetz
Reg. No. 37,505

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 9411-3834
Tel (650) 326-2400
Fax (650) 326-2422

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